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Students Abstract Collection
Alphabetical order according to presenting author
List of Abstracts (in alphabetical order)

1. A NEST-simulated cerebellar spiking neural network driving motor learning  
   **Alberto Antonietti, Claudia Casellato, Csaba Erö, Egidio D’Angelo, Marc-Oliver Gewaltig, Alessandra Pedrocchi**

2. Using Predictive Pre-Clinical Modeling to Improve Efficacy of Cancer Drug Selection  
   **Maria Aseeva, Marisa Torres, Jonathan Allen**

3. Towards a second-generation and physiologically realistic model of critical oscillations (CROS 2.0)  
   **Arthur-Ervin Avramiea, Richard Hardstone, Jan-Matthis Lueckmann, Jan Bim, Marco Aqil, Huibert D. Mansvelder, Klaus Linkenkaer-Hansen**

4. Analysis of Cortical Surfaces via Sparse Representations to Monitor HD progression  
   **Andrea Bertarini**

5. Modeling Gamma Oscillations in Adaptive Exponential Integrate-and-Fire Networks  
   **Eduarda Demori Susin, Alain Destexhe**

6. Towards mathematical modelling of the role of glial cells in cerebral interstitial fluid movement  
   **Ada Johanne Ellingsrud**

7. Trying to divide the ventral intermediate nucleus of the thalamus into functionally distinct subregions differentially involved in motor learning and essential tremor  
   **Amr Farahat**

8. Behavioural and Biological Responses to Moral and Conventional Violations in Non-offenders with Varying degrees of Psychoticism  
   **Natalia Filvarova**

9. Real-Time Response of Spiking Neural Networks to Dynamic Constraints  
   **Gabriel Fonseca Guerra and Steve Furber**

10. Multi-Electrode Array (MEA) electrophysiology: an overview  
    **Alessandro Furia**

11. Association between cognitive decline and loss of microstructural integrity of the cerebral white matter in patients with glioblastoma multiforme  
    **Xenia Hautmann**

12. Abnormal resting state EEG dynamical patterns in ADHD measured with Recurrent Neural Networks  
    **David Ibañez-Soria, Aureli Soria-Frisch, Jordi Garcia-Ojalvo, Giulio Ruffini**

13. Understanding network level changes in Multiple Sclerosis: Relationships with cognitive dysfunction  
    **Danka Jandric**

14. Detecting Schizophrenia from MRI Images Using Machine Learning
Maria Kesa
15. Study of neuronal activity amygdala of rat's after immobilization stress and under the influence of taurine
Khachatryan V.P., Danielyan M.H.

16. The influence of physical exercise on cognitive functions and neuroplasticity in healthy individuals and in selected patients. Biochemical, neuroimaging and neuropsychological assessment
Klopacki Jan, Borkowska Alina

17. Machine Learning and Pattern Recognition for the development of diagnostic and clinical prognostic prediction tools in psychiatry, borderline mental disorders, and neurology
Alexander Bernstein, Mikhall Gelfand, Evgeny Burnaev, Ekaterina Kondratyeva

18. Modulation of TrkB-mediated neuronal plasticity by receptor-like protein tyrosine phosphatase sigma (PTPR#)
Angelina Lesnikova, Caroline Biojone, Eero Castren

19. A computational model of motor cortex activity in response to transcranial magnetic stimulation
Alessandro Loppini, Christian Cherubini, Simonetta Filippi

20. Seizure self-prediction in epilepsy
Michael Mackay, Roger Whittaker, Marcus Kaiser

21. Computationally efficient cerebellar neural models reproducing characteristic spike response patterns
Milagros Marín Alejo, Jesús Garrido, María José Sáez-Lara, Eduardo Ros

22. Competition Models of motion integration and depth ordering in Multistable perception of moving plaids
Camilo Miguel Signorelli

23. Pathological increase of the spectral centroid of resting state BOLD signal from the salience network in MDD
Anja Ries, Chun Meng, Christian Sorg, Afra Wohlschläger

24. Novel concept of intrinsic ignition characterises the broadness of communication in different brain states or conditions

25. Bistability and complexity within the sleeping brain: simultaneous intracranial EEG and high-density scalp EEG recording

26. Biomarkers for Treatment Resistant Depression
Malak Saada

27. The impact of music on the brainwave oscillations in children

Sakalauskaite D, Praninskiene R


Daniel Bug*, Steffen Schneider*, Anne Grote, Eva Oswald, Friedrich Feuerhake, Julia Schuler, Dorit Merhof

29. The Reorganization of Functional Architecture in the Early Stages of Parkinson’s Disease

Noora Tuovinen, Klaus Seppi, Francesco de Pasquale, Christoph Müller, MDa; Michael Nocker, Michael Schocke, Elke R Gizewski, Christian Kremser, Gregor K Wenning, Werner Poewe, Atbin Djamshidian, Christoph Scherfler, Morinobu Seki
A NEST-simulated cerebellar spiking neural network driving motor learning

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The brain organization is optimized to drive adaptive behavior. A key role in the control loop is played by the cerebellum, which implements prediction, timing, and learning of motor commands, through complex plasticity mechanisms. However, how plasticity and neuron properties are engaged during the behavior is still unclear. Cerebellar properties emerge in associative sensorimotor paradigms, such as the Eye Blinking Classical Conditioning (EBCC). In silico simulations based on realistic computational models are fundamental to investigate the physiological mechanisms responsible for the behavior.

We developed a realistic cerebellar network running on NEST. NEST is a simulator for spiking neural network models, focused on the dynamics, size, and structure of neural systems by the generation of complex networks of single-point neurons. We built a network tailored on the mouse cerebellum. The network is made of 71'440 neurons: 250 Mossy Fibers (MF), 5’000 Glomeruli (Glom), 65’600 Granular Cells (GR), 100 Golgi Cells (GO), 400 Purkinje Cells (PC), 40 Inferior Olive cells (IO), 50 Deep Cerebellar Nuclei (DCN). Three of these synaptic types could undergo specific plastic modifications, in particular, Long Term Potentiation and Depression on different time scales. The numbers of the different cells and the connectivity were taken from measurements found in the neurophysiological literature. The model was tested with a simple closed-loop simulation of the EBCC, to check the functionalities of the network in a learning task. In the EBCC, a Conditioned Stimulus (CS) precedes an Unconditioned Stimulus (US) by a fixed time interval. The cerebellum is able, after repeated presentations of CS and US paired during the acquisition phase, to anticipate the US onset, this action is called Conditioned Response (CR). During the extinction phase, only the CS is provided. The network, thanks to the distributed plasticity, was able to learn the CS-US temporal association during the acquisition trials, with a fast acquisition towards 80% values, and to rapidly unlearn the association during the extinction trials. As future work, we are going to extend this model to a large-scale reproduction of the mouse cerebellum (more than 39 million neurons) and to test the network capabilities in more complex paradigms and in pathological conditions.
Using Predictive Pre-Clinical Modeling to Improve Efficacy of Cancer Drug Selection

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The advent of next-generation sequencing potentiates the identification of clinically actionable genomic changes implicated in cancer. The BAASiC initiative aims to integrate supercomputing into drug sensitivity prediction models to infer relationships between genomic mutations and drug effectivity. The predictions of such models are improved with the addition of large-scale data. This has large implications in how cancer treatments are developed, tested, and prescribed on an individual basis.
Towards a second-generation and physiologically realistic model of critical oscillations (CROS 2.0)

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Criticality is a state of dynamic systems, where the complex interaction of system components leads to the emergence of spatiotemporal patterns characterized by scaling laws. Hallmarks of criticality in the brain have been identified in scaling laws of neuronal avalanche statistics, long-range temporal correlations (LRTC) [1,2], as well as 1/f noise in the power spectrum. Evidence of altered LRTC in major depressive disorder [4], Alzheimer [5] and epilepsy [6], has urged the study of mechanistic prerequisites of the critical state, as well as of its functional implications. Here, computational models are of utmost importance, as they allow for complete control and access to the neural dynamics. In this direction, the critical oscillations (CROS) model [3] has provided with unique insights, by connecting excitation-inhibition balance with the two forms of criticality previously observed in the brain: power-law scaling in neuronal avalanches and LRTC. However, the neuronal model in CROS is an abstraction of neuronal dynamics that lacks physiological quantities, and as such it is not straightforward to relate and constrain parameter values with physiological data. Therefore, we are currently implementing a state-of-the-art neuron model, coined the leaky-integrate and fire, where the membrane potential is explicitly modeled, along with conductance-based synapses and a leaky term.

The probabilistic character of the original CROS model enables it to exhibit a rich diversity of spatiotemporal patterns. By contrast, the LIF model is deterministic, which means that neurons within a local neighborhood tend to respond similarly to a common neural input. After extending LIF with normally distributed membrane potential noise and short-term plasticity [7], the model could produce the rich diversity of spatiotemporal patterns characteristic of criticality. Interestingly, we found that both the old and the new model, the dynamic range is optimal when the network is operating at criticality [8]. Moreover, both models show a dependence of criticality on excitation/inhibition balance, suggesting that this relationship is not model-dependent, but instead generic to critical systems.


Huntington Disease is a genetic and neurodegenerative disease that dramatically reduces the volume in different brain regions, and that leads to motor, cognitive impairments and emotional disorders. The disease is caused by a single gene mutation, and by a specific genetic test it is possible to predict, even before the birth, the disease and estimate his onset age.

Medical research is currently focused in delivering treatments able to slow down the neurodegenerative process, or postpone the onset age. These studies require effective bio-markers to quantitatively assess the disease progression. Unfortunately, at the moment there are no effective bio-markers that can reliably characterize the disease in its early stages, before it becomes manifest.

Anatomical brain imaging, in particular MRI, can certainly provide promising bio-markers: from MRI scans it is possible to measure the thickness/volume of brain regions and cortical surfaces. Medical literature reports that these measurements have shown good correlation with the disease progression, but also those bio-markers cannot identify early stages of the disease, when changes are more subtle and difficult to perceive.

In this thesis we investigate a new, patient-specific bio-marker, which is obtained by analyzing cortical surfaces by means of an anomaly-detection algorithm. In particular, we learn a model yielding sparse representations of the shapes/structures characterizing the cerebral cortex of each patient. These learned models are used in longitudinal scans to quantitatively assess how much structures characterizing the cerebral cortex, depart from the original conditions.

We have validated the learned model and tested our bio-marker over a set of 20 early HD patients (4 visits each), and a set of 8 control patients (7 visits each). The data set was pre-processed by IBM, with which we collaborate, using FreeSurfer.

Our results indicate that the model is able to well capture the structure of the cortex, but that the biomarkers are not stable enough across different visits to provide meaningful enough information with respect to the cortical thickness.
Modeling Gamma Oscillations in Adaptive Exponential Integrate-and-Fire Networks

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Gamma rhythms are observed in both waking and sleep states, in different species and in several brain regions. However, despite of the large number of studies about this phenomenon, the exact mechanism of their genesis and coexistence with other brain states is still largely unknown. Recent findings in human data showed that, with respect to the oscillatory gamma cycle, during slow wave sleep and awake states, there is a higher proportion of inhibitory neurons spiking with higher frequency, in contrast to the excitatory population. Furthermore, the inhibitory neurons fire earlier than excitatory ones on average, suggesting that inhibitory cells play a key role in the generation of gamma rhythms in humans. Here, we use modeling to attempt to reproduce some of these recent findings, with the aim to understand the genesis of gamma oscillations in humans, and ultimately, how such oscillations are involved in processing external stimuli. We first used a generator of gamma oscillations from interconnected inhibitory neurons. Next, we embedded this oscillator in a network of Adaptive Exponential (AdEx) neurons, displaying synchronous states similar to in vivo recordings. We describe how the inclusion of gamma generator circuits allows the whole network to display synchronous irregular gamma oscillations with some features consistent with recordings in humans.
Towards mathematical modelling of the role of glial cells in cerebral interstitial fluid movement

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Brain tissue is composed of networks of interstitial spaces, blood vessels, compartments filled with cerebrospinal fluid (CSF) and primarily two classes of cells: neurons and glial cells. The neurons transmit information through electrical and chemical signals, and have been studied extensively over the last decades. The glial cells, on the other hand, were for long considered passive bystanders of neural activity, and have therefore not received the same attention. However, recent research efforts indicate that the glial cells may have a far more important and active role than originally assumed. Particularly, the astrocytes (star-shaped glial cells) seem to have key roles in the volume control of the ECS and brain water clearance.

Within the endfoot barrier of astrocytes near the perivascular spaces surrounding the blood vessels, there is a high concentration of the channel membrane protein aquaporin-4. The AQP4 proteins form structures in the astrocytic membranes allowing for highly efficient water transport, and play an important role in mechanisms underlying volume and water homeostasis in the brain. The water transport through AQP4 is driven by osmotic pressure gradients, primarily regulated by movement of ions in the brain tissue. However, our current understanding of these mechanics is far from complete.

As measuring the phenomena is difficult, both due to technical and ethical challenges, mathematical and numerical modelling could give new insight. Several researches have proposed models for glial membrane dynamics and ion transport (Osteby et al. 2009; Halnes et al. 2013; Mori, 2015). However, these models primarily address electrochemical processes at the cellular level, leaving modelling of glial dynamics and their role in interstitial fluid flow largely open.

In this presentation, I will give an overview of existing hypotheses surrounding glial cell dynamics and the role they are believed to play in the clearance of metabolic waste in the parenchyma, as well as current modelling techniques. I will also present objectives for new models we aim to develop accounting for interaction between glial cells and their role in macroscale fluid flow.
Deep brain stimulation (DBS) of the ventral intermediate (VIM) nucleus of the thalamus is a well-established method for treatment of essential tremor (ET). The precise location of the stimulation is critical for the optimal control of the tremors and also for avoiding potential side effects. Several studies have pointed out an overlap in the neural correlates of ET and motor learning. It has been shown also that DBS treatment of ET has different effects of motor learning skills of the patients. We hypothesise that there might be an optimal electrode location that would maximize the tremor control and minimize the potential impairment of motor learning. We propose a 7T fMRI study to address this question.
Behavioural and Biological Responses to Moral and Conventional Violations in Non-offenders with Varying degrees of Psychoticism

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According to Eysenck’s theory of criminality (Eysenck & Eysenck, 1970), criminal behaviour can be explained by personality traits. Research has shown that offenders score high on the psychoticism trait of the model (Eysenck & Gudjonsson, 1989). Additionally, it has been reported that offenders have difficulties judging the moral and conventional acceptability of social situations. In the present study these two facets are brought together to examine behavioural (accuracy and RTs) and biological (GSR) responses to moral and social violations of individuals who have different psychoticism scores, but who are not criminal offenders. It was found that individuals with high levels of psychoticism responded more slowly when making such judgements and displayed no reactivity to violations in their Autonomous Nervous System. Additionally, speed of moral judgements was mediated by the GSR. Implications for current theories and suggestions for future research are made.
Real-Time Response of Spiking Neural Networks to Dynamic Constraints

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Some theoretical works have demonstrated how noise can be used by spiking neural networks (SNNs) as a computational resource, especially in the context of hard constraint satisfaction problems (CSP). Noise allows the SNNs to perform stochastic computations which could explain some of the intrinsic mechanisms used by the brain in its interaction with the environment. Recently, we have been able to implement a real-time version of such computations using the spiking neural network architecture (SpiNNaker) neuromorphic hardware. In this work, we present a time-dependent version of such computations in which the network interacts with dynamic constraints and adapts its own dynamics to satisfy them. We analyse the stochastic processes and convergence times within the framework of information theory. This work is especially important in the fields of neuroprosthetics and robotics where the hardware needs to take decisions in real time while interacting with complex environments.
Multi-Electrode Array (MEA) electrophysiology: an overview
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Multi-Electrode Array (MEA) devices are increasingly being used for extracellular measurement of electrophysiological signals (e.g. action potentials, local field potentials) of excitable cells. Their usefulness has led to gradual improvement in materials and production, for instance introducing flexible, all-polymer MEAs employing micro-channels in poly(dimethylsiloxane) (PDMS), coated by films of polystyrenesulfonate-doped poly(3,4-ethylenedioxy-thiophene) (PEDOT:PSS). These reduce adverse biological effects when used in vivo, e.g. inflammation and cytotoxicity (Blau et al., Flexible, all-polymer microelectrode arrays for the capture of cardiac and neuronal signals, Biomaterials 2010).

A MEA chip consists of multiple electrodes (e.g. 60) which can be arranged with a particular geometry (for example hexagonal, square). The dimensions and distance between electrodes is in the order of micrometers. The chip allows for coupling with in vitro cells.

Concerning in vitro experiments, primary neuronal cultures can be grown on the chip following coating with laminin and poly-l-lysine. During my project at IIT, a culture from cortex of embryonic rats was prepared by using a “complete Neurobasal medium” (consisting of Neurobasal medium, B27, alanyl-glutamine (Gluta-MAX) and penicillin/streptomycin).

Several softwares are used to acquire and elaborate data from MEA devices. One of them is MC_Rack (Multichannel System), which allows for filtering and graph plotting. Statistical analysis can then be employed to determine data significance.

Apart from the above case, MEA measurements are used in a wide variety of cases, including studying of photosensitive tissue (e.g. retina) and electrical activity of cardiomyocytes. Biological implants for spinal cord or brain-machine interfaces are also possible applications.
Association between cognitive decline and loss of microstructural integrity of the cerebral white matter in patients with glioblastoma multiforme

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The glioblastoma multiforme is the most common malignant brain tumor of adults.

Patients with this tumor frequently suffer from cognitive decline, which usually progresses during the course of the disease and treatment and has an huge influence on their quality of life.

Since these patients are prone to a plethora of neurotoxic effects associated with the brain tumor and its treatment, a multifactoral genesis of the cognitive decline should be assumed: The tumor itself as well as surgical resection might damage functional neuronal tissue. Moreover, whole-brain irradiation and chemotherapy with temozolomide exert further neurotoxic damage to the tumor region and to the global cerebral tissue.

In our study, we aim at a specific characterization of the occurrence and further course of cognitive decline and its morphological substrate in patients with glioblastoma multiforme.

Therefore, a specific neuropsychological test battery (defined by the NOA-19 study) will be carried out preoperative, postoperative and every 3 months after surgical resection. MR imaging including diffusion tensor imaging (DTI) will be carried out on the same time points to identify the loss of integrity of the white matter. This imaging method measures the diffusion of water molecules in the brain tissue. Water molecules cannot move unimpeded in axons of the white matter but are bordered by cell membranes. Hence, they move mainly in the direction of neural tracts.

Several neuropsychological parameters will be correlated with fractional anisotropy (a DTI parameter), using the software tract-based spatial statistics (FSL, Oxford). The localization of these positive correlations between affected microstructure of white matter and specific neuropsychological deficits will be identified on a tract skeleton.

Furthermore, the integrity of three parts of the callosal body will be characterized by standardized fiber tracking and also correlated with neuropsychological parameters.

We hypothesize a decrease of fractional anisotropy after surgical resection, and after adjuvant treatment and an association between reduced fractional anisotropy and deteriorated neuropsychological function.

Since our study is part of the multicenter NOA-19 study (Department of Neurosurgery, University Hospital Cologne, Germany), the Germany-wide number of cases for our preoperative correlations will be about 50 patients.
References:


Abnormal resting state EEG dynamical patterns in ADHD
measured with Recurrent Neural Networks

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Attention deficit hyperactivity disorder (ADHD) is one of the most common neurodevelopmental and psychiatric disorder in childhood. Difficulties in the diagnosis of ADHD advocate for the analysis of electrophysiological signals as they may reveal abnormal brain patterns in ADHD. In the last decades, resting state electroencephalographic (EEG) measures have been used to document underlying neurophysiological dysfunction in ADHD. Most reported findings have shown that ADHD-diagnosed children present an increased power in fronto-central regions in slow frequencies (theta band) along with decreased power in fast frequencies (beta band). The brain is a complex system that generates non-stationary EEG patterns. This dynamic and chaotic behavior advocates for the use of non-stationary techniques for EEG feature extraction and classification. Here a novel dynamical approach to quantify changes between eyes closed (EC) and open (EO) resting-state EEG within each subject is presented. Our hypothesis is that the differences between these two conditions may diverge in the ADHD population. Recurrent neural networks (RNN), in their Echo State Network (ESN) modality are trained in a two-class regression problem to distinguish between EO and EC conditions. Dynamical changes between conditions are studied at theta1 (4-6 Hz), theta2 (6-10 Hz), alpha1 (8-11 Hz), alpha2 (10-13 Hz), beta1 (13-20 Hz), beta2 (20-30 Hz), gamma1 (25-35 Hz), and gamma2 (35-45 Hz) bands. Amplitude information of the temporal dynamics is removed via standardization before training. Changes are measured as the error between the ESN output and the binary EO/EC ground truth signal. 53 children aged 7-11 years participated in this study including 22 ADHD-diagnosed subjects and 31 age-match healthy controls (HC). 6 electrodes measured the participants’ brain response in fronto-central areas. The experimental protocol consisted of two independent 3-minute eyes open and closed recordings. Results showed that HCs presented larger differences between EC/EO conditions. Statistically significant differences were only found at theta1, beta1, and beta2 frequency bands (Wilcoxon Rank Sum test). Phase amplitude coupling analysis results reported a reduced beta-phase gamma-amplitude coupling in the ADHD population. Our results prove the existence of alterations in the spontaneous EO/EC dynamics in the ADHD population. The proposed methodology may complement classical brain connectivity and complexity analysis: 1) functional connectivity at slow frequencies is lower in EO and 2) complexity of EEG at low frequencies is increased in EC. These and other dynamics may be altered in ADHD population as the distinction between conditions is smaller. An interesting discovery is that these alterations were found statistically significant at the same frequency bands as state-of-the-art stationary power ADHD biomarkers.
Understanding network level changes in Multiple Sclerosis: Relationships with cognitive dysfunction

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Multiple Sclerosis (MS) is a leading cause of neurological disability in young adults. Around 40-70% of patients present with cognitive impairment, even as early as disease onset. It is well documented that cognitive impairment is debilitating for patients and strongly related to progression of physical disability. However, the mechanisms underlying cognitive impairment are currently not well understood. Emerging evidence from network neuroscience suggests that cognitive impairment may be driven by microstructural changes in normal appearing grey and white matter. In this study, we will undertake a number of complementary novel neuroimaging methods to determine the neural network changes underlying cognitive impairment in early MS. Additionally, we will investigate whether early changes in sodium accumulation in specific brain regions contribute significantly to network breakdown. The results have the potential to provide new prognostic markers which could enable personalised treatment decisions and thus improved outcomes for MS patients with cognitive impairment.
Detecting Schizophrenia from MRI Images Using Machine Learning

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The advent of measurement techniques for biological systems such as gene expression arrays and magnetic resonance imaging has brought with it a host of challenges for realizing their medical potential. Medicine could benefit greatly from the predictive information contained in this data, but measurement alone is not sufficient for the full utilization of these modalities. The naked human eye is limited in discerning the patterns corresponding to the presence or risk for disease from high-dimensional arrays of numbers in gene expression profiles or complex images of the structure of the human brain. There is an acute need for computer algorithms that extract clinically useful information from data. This talk is concerned with machine learning algorithms that enable the utilization of and facilitate knowledge discovery from complex biological data. The aim of the study on which this presentation is based was to “learn” a model that would give a compact representation to cortical thickness features extracted from MRI images, which are a biomarker for schizophrenia. We employed a probabilistic generative model, called Counting Grids, that embeds similar high-dimensional data points in close proximity on a two-dimensional surface. This embedding is a visualization of the data, thus allowing the human visual system to tap into the information contained within it. This is particularly relevant in the clinical setting of schizophrenia diagnosis, where neuroimaging measurements are currently not employed in assisting the diagnostic decision. We employed kernel methods to carry out classification on model parameters, reaching state of the art classification accuracies. This is a proof that the learned model parameters contain the information relevant to the presence of disease (such as schizophrenia and different types of cancer), but is arguably less useful in the clinical setting, because the real need is in making the information in the data available to the doctor who can integrate it with other relevant evidence that he observes, not in making the diagnostic decision for the professional.
Study of neuronal activity amygdala of rat's after immobilization stress and under the influence of taurine

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The cause of stress can be various adverse factors of daily life associated with the emergence of negative emotions. Stress leads to long-term changes in many indicators that characterize the functional state of the organism at all its structural levels. The amygdala is actively involved in the processes of neuronal rearrangements during stressful actions. Therefore, it seems relevant to study the nature of the changes in the parameters of the background impulse activity of neurons of the amygdala of the brain after immobilization stress. In stressful situations, there is a deficiency of taurine in the organism, and to improve the nervous activity it is necessary to use it, which probably has a modulating effect on the functional state of the organism and contributes to the stabilization of the activity of the nervous system.

The goal of the studies was an electrophysiological study of the effect of taurine on the parameters of the background impulse activity of rat brain neurons of amygdala after immobilization stress. In semichronic studies in rats, a change in the ratio of excitatory and depressant post-stimulatory manifestations of amygdala activity to tetanic stimulation of the hippocampus was studied in the norm, in dynamics after acute immobilization stress and under taurine protection (for 7 days).

Microelectrophysiological experiments with an extracellular recording of single amygdala neurons were performed in rats in groups: norm and after 1 day, 90 days and 7 days after acute immobilization stress with the systematic taurine administration. Acute immobilization stress was caused by fixing the animal on its back for two hours. To detect the protective effect of taurine, an aqueous solution of taurine (50 mg/kg) was injected directly into the animals immediately after the stress for 7 days. The background impulse activity and the induced spike activity of single amygdala neurons were recorded extracellularly during high-frequency stimulation of the hippocampus in intact rats, after immobilization and under the influence of taurine. A software mathematical analysis of the single spike activity of amygdala neurons was carried out according to a specially developed algorithm.

To study of the morphofunctional state of the amygdala of rats we use the new histochemical approach of detecting the activity of Ca 2+-dependent acid phosphatase developed by I.B. Meliksetyan. This methodical approach is based on detection of intracellular phosphorus-containing substances playing the key role in the metabolic energetic processes aimed at preservation and self-reproduction of vital systems.

Immobilization stress leads to a significant change in the parameters of activity of neurons of the amygdala. In acute experiments on intact Albino rats, 1, 90 days after immobilization stress and after 7 days after stress with taurine injection the recording of amygdala single neurons activity in response to high-frequency stimulation of hippocampus by means of on-line selection and software mathematical analysis, based on depressor and excitatory tetanic and post-tetanic effects, we revealed the following: in neurons of amygdala, in comparatively with the norm, after strengthening above the norm of post-stimulus excitation by 1 day, its sharp decrease by 90 days is shown, and its significant
increase when combined with taurine (Fig. 1 A). After 1 day of testing, there was a drastic decrease in depression, and on the 90th day, on the contrary, increased depression, but the same sharp decrease when combined with taurine (Fig. 1 B). Thus, in the amygdala, in comparison with the norm, an increase in tetanic excitatory effects on day 7 after stress in combination with taurine and a powerful increase in tetanic depressor effects on day 90 after stress (Fig. 1 A, B). In comparatively with the norm, under the influence of taurine to the 7th day after stress, the excitation sharply increases and the depression sharply decreases, which indicates the ability of taurine to promote the tendency of restoring the ratio of multidirectional post-stimulus effects.

![Graph A](image1.png)

![Graph B](image2.png)

Fig.1. The percentage of excitatory and inhibitory effects in neurons of the amygdala (Amygd.). On the tetanic stimulation of the hippocampus on days 1, 90, after stress and under the protective effect of taurine on day 7 after stress, compared with the norm.

Histochemical data were obtained confirming the neuroprotective efficacy of taurine revealed in this electrophysiological study and indicating its possible involvement in the mechanisms of recovery and remodelling by improving the survival of neurons damaged by stress and participating in regulating brain plasticity through neurogenesis (Fig. 2 A-L).
Fig. 2 The effect of taurine on the neurons of the amygdala of rats after immobilization stress. (A-C - is the norm, D-F - 5 days after the stress, G-I - after 3 days of taurine injection after stress, J-L - after 7 days of taurine injection after stress; black arrow - chromatolysis, white arrow - ectopic nucleus, arrowhead - the submembrane location of AP). At 3-day (G-I) and 7-day (J-L) exposure to taurine, neurodegeneration was demonstrated in comparison with damaged amygdala (D-F) neurons 5 days after immobilization. Magnification: 40 (a); 100 (A, D, G, J); 400 (B, E, H, K); 1000 (C, F, I, L).

Thus, the analysis of electrophysiological data allows us to conclude that taurine has a neuroprotective effect on the neurons of the amygdala on the 7th day already with the systematic introduction of taurine immediately after stress, since under the influence of taurine in neurons of the amygdala is an increase in excitatory and a sharp weakening of inhibitory effects, in comparatively with immobilization. The results of studies suggest that considering the small force of pathological effects, for the prompt and energetic taurine treatment a significant part of cellular changes induced by psychoemotional stress can be prevented because of the reversibility of morphological and functional abnormalities.
The influence of physical exercise on cognitive functions and neuroplasticity in healthy individuals and in selected patients. Biochemical, neuroimaging and neuropsychological assessment

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In spite of the famous work of Santiago Ramón y Cajal (Ramon y Cajal, 1895), until the 1960s it was an accepted theory in neuroscience that the adult nervous system is rather hard-wired and had probably a rather limited capacity to change (Grossman, 1967). However this knowledge is an example of how new discoveries may change our dogmas. Today we know, both from animal and human studies that the brain is influenced by the environment and is constant plastic change. The process of environment based reorganization of human brain is called neuroplasticity. Discovery of this phenomenon has led to numerous studies trying to answer the question how to affect those mechanisms and stimulate positive changes for example by enhancing the process of learning or slow down the age-related cognitive decline. Throughout last decades many studies reporting influence of physical activity on the functions of central nervous system has been published. There is a wide range of research in this topic (Hitting, 2013). Both acute and chronic effects of exercise as well as the influence of cardiovascular fitness on the course of neurological conditions had been tested and seem to have a beneficial effect on cognitive functions. However the processes that underlay this relationship look very complex. Most of the studies aiming to define those mechanisms are conducted on animals and suggest that possible explanations include inducing of neurogenesis, reorganisation of synaptic connections, increased release of neurotrophins and neurotransmitters as well as stimulation of angiogenesis. This theoretical introduction is a basis for the further studies. The first aim of the studies is to define the impact of different kinds of physical exercise on cognitive functions in healthy individuals and in cooperation with clinics, in patients with selected neurological conditions. Another planned research is going to assess the correlation between the cardiovascular fitness, measured with maximal oxygen consumption (VO2max) as a gold standard, and the course of neurodegenerative diseases such as Multiple Sclerosis and Alzheimer's disease. Moreover studies to be conducted will include neuroimaging techniques like functional magnetic resonance (fMRI) and diffusion tensor imaging (DTI) and biochemical measurements of neurotrophins (e.g. BDNFα, IGF-1) depending on the technical and financial possibilities. Results of this research are expected to expand the knowledge about the mechanisms mediating beneficial cognitive effects of physical exercise. Furthermore the outcome of this studies may serve for the clinical practice, as the confirmation of the positive effects of exercise on the course of neurological diseases can lead to introduction of new means of prevention and treatment.
Machine Learning and Pattern Recognition for the development of diagnostic and clinical prognostic prediction tools in psychiatry, borderline mental disorders, and neurology

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Machine learning is a collection of methods derived from artificial intelligence and statistical learning. These methods have been a key facilitator in developing biomarkers from brain-imaging and other clinical data as they have proven effective at tackling the analytic challenges of high-dimensional data.

The final project goal is to develop new and to adapt the existing modern machine learning methods and techniques, including our own ones, for applying them to brain-imaging and other clinical data about patients with mental disorders (psychiatry, borderline mental disorders, and neurology) for discovering new biomarkers, dependencies and regularities and using them in diagnostic and clinical prognostic prediction. The modern methods and techniques such as Deep Neural Networks, including innovative 3D convolutional networks, manifold learning and Bayesian generative modeling, and others, will be used in the project. In the first project stage (2017), concrete project objective is the solution of actual biomedical problem: with the use of machine learning technologies, to find new features, biomarkers and predictors of epilepsy and depression in MRI studies, which will in turn contribute to improving the diagnostics and treatment of the diseases.

The obtained algorithm will allow us to advance in diagnostics and neuroimaging of other neurological and mental disorders that are of high social significance, which determines the necessity of investigating new possibilities of early detection and treatment.
Tropomyosin receptor kinase B (TrkB) is a kinase receptor activated by neurotrophin brain-derived neurotrophic factor (BDNF). TrkB signaling plays a major role in several functions in the central nervous system, such as cell survival and proliferation, the fate of cell during differentiation, axon and dendrite sprout, synaptic strength and plasticity. TrkB signaling is also crucial for cognitive processes, such as learning and memory, for stress coping and resilience to development of mental illnesses. Aberrant TrkB signaling has been shown to be implied in a variety of neurodegenerative, psychiatric and proliferative disorders, as well as in cancer. Activation of TrkB through phosphorylation of its tyrosine residues is relatively well understood and described in the literature. However, little is known about other mechanisms modulating its signaling. Dephosphorylation seems to be a natural tool to counterbalance TrkB phosphorylation-induced activation. Receptorlike protein tyrosine phosphatase sigma (PTPR#) is a plausible candidate to implement Trk dephosphorylation. PTPRs have been shown to interact with and modulate TrkB receptors activity, and BDNF exposure has been demonstrated to regulate this interaction. There is evidence for PTPRs co-expression with Trk proteins, including TrkB. Moreover, preliminary experiments from our group suggest that PTPR# is present in TrkB-bound complex of proteins. PTPR# has also been recognized to be involved in neuronal plasticity processes through its interaction with perineuronal nets (PNNs), another important regulator of the CNS plasticity. It has been shown to be a receptor for chondroitin sulfate proteoglycans (CSPGs), major component of PNNs and a well-known inhibitor of axonal growth and regeneration. Functional ablation of PTPR# has been demonstrated to promote plasticity mechanisms as PTPR# knock-out mice display substantial elevation of axonal regeneration after injury. Mechanisms of functional interplay between PNNs and TrkB signaling are yet to be fully established; however, we hypothesize that PNNs could restrain TrkB signaling through PTPR#. Unraveling the role of PTPR# in TrkB-mediated neuronal plasticity could have immense effect on our understanding of plasticity mechanisms in the CNS in general and could potentially introduce new therapeutic target for patients whose conditions imply neurodegenerative and psychiatric disorders, as well as brain injuries.
A computational model of motor cortex activity in response to transcranial magnetic stimulation

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Several experimental methods have been proposed and developed to investigate the functionality of the brain, both in physiological and pathological conditions. Among these, transcranial magnetic stimulation (TMS) was used to study the electrical activity evoked in the motor cortex in response to localised stimuli [1,2]. Experimental recordings of the corticospinal tract show that such evoked activity is stereotyped and consist of descending volleys separated by a delay of about 1.5 ms. The first wave, “D-wave”, comes from the direct activation of the axons of L5 cortical neurons from which originates the pyramidal tract. Later waves, “I-waves”, are generated by trans-synaptic indirect activation of L5 pyramidal neurons. Interestingly, the shape of such train of waves is significantly altered by the specific stimulation protocol adopted. Based on this, it was hypothesized that different neuronal pools contribute to volleys generation, and a model of motor cortex circuitry was introduced [3]. In this work, we test such circuit by a computational modelling approach. In line with other published studies [4], we model different populations of cortical neurons based on a Hodgkin-Huxley-type formalism, including L2, L3 and L5 neurons. The L2 and L3 neuronal pools comprise inhibitory and excitatory units, which show a spiking or intrinsic bursting behaviour. Such populations project synapses onto the L5 neurons based on the proposed feed-forward circuit. We simulate different TMS protocols by selectively stimulating the neuronal network, and we analyse the evoked activity in the axons of the L5 neurons. Numerical results, coming from the integration of a large number of single L5 neuronal responses, are finally compared with the available experimental recordings of D-I waves. Reconstructed signals support the idea that the activity of different neurons is responsible for the generation and specific modulations of descending volleys. Such modelling can be used in the future to investigate D-I waves in pathological scenarios such as stroke, possibly inferring neuronal damage based on the evoked descending activity. Further expansions of the model taking into account neuromuscular coupling and motor units activity will also be considered with the aim to investigate the effect of D-I waves modifications on muscle contraction.

Seizure self-prediction in epilepsy

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Any study into seizure self-prediction confronts two contradictory viewpoints; that seizures strike out of the blue, leading to the social and legal sequelae of epilepsy, and that patients widely report having some ability to predict their own seizures. Current evidence suggests a significant proportion of patients may be able to appraise their seizure risk over a time window of several hours, and that we may be underestimating this ability in the population. This ability is related to mood and mood disturbance, as well as the occurrence of prodromal symptoms, and suggests an underlying mechanism which drives prodromal symptoms, mood disturbances and seizure risk which we hypothesise to be disruptions in cortical inhibition. We have been developing a simple visual psychophysics test which can measure the level of surround inhibition in visual cortex as a proxy measure of cortical inhibition and are developing a smartphone application to collect longitudinal data on surround inhibition, mood and seizure risk. Our aim is to investigate further the relationship between seizure risk and mood disturbance, whether there is any common relationship with cortical inhibition, and whether we can augment patients' ability to predict seizure risk.
Computationally efficient cerebellar neural models reproducing characteristic spike response patterns
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Electrophysiological investigations of the cerebellar cortical neurons (mossy fibers, granule cells, unipolar brush cells, Purkinje cells, Golgi cells, between others) have reported several characteristic firing patterns (i.e. spike bursts and resonant firing in granule cells [1], late response firing in unipolar brush cells [2], pacemaking firing in the Golgi cells [3] that describe the inherent neural dynamics of these neurons. These firing features play a key role in a wide variety of sensorimotor information processing primitives, as synchronization, rhythmicity and learning [4]. Simulation of models embedding a combination of channels and specific interneuron synapses allow the reproduction of these specific neural characteristics. Experimental recordings accounting for the effects of pharmacological drugs and genetically modified species enable the creation of phenomenological conductance-based neuron models mimicking the electrical behavior of real neurons with great accuracy. However, the simulation of these detailed models requires a large number of differential equations to be solved at each time-step, which is computationally very expensive. Therefore, the simulation of millions of these neurons is still far from being possible. On the other hand, the generation of efficient computational models usually neglects inherent neural dynamics, producing lighter (efficient) but inaccurate neuron models. Aiming to reduce drastically the computational cost in simulating each neuron, while identifying and integrating its functional features, a new working methodology is presented by converting detailed complex models to simpler neuron models while keeping similar dynamics. This is achieved by automatically adjusting the set of neuron model parameters with evolutionary algorithms. In conclusion, we explore the simplification of complex Hodgkin and Huxley neural models to computationally efficient neuron models but mimicking its intrinsic neural characteristics. These neuron models will allow large-scale network models to embed realistic model features and unveil the effect that complex firing patterns play in cerebellar information processing.


Tri-stability perception of ambiguous moving plaids can give informative insight about how the visual system deals conjointly with two computational challenges among the most important in perceptual organization: motion integration vs. segmentation and depth ordering. Experiments and models are needed to better understand this visual organization; however, it is also needed to reduce the number of free parameters to achieve this goal in complex architectures. Thus, three different conditions were measured in the same subject to restrict simulations and find the equi-dominance regime in each condition: (1) bistable depth ordering in purely transparent plaids, (2) coherent and transparent motion in bistable plaids (using occlusion cues) and (3) tristable plaids. Mean duration was not correlated across subjects between the two bistable systems and the duration of transparency percept was longer in depth bistability than tristability. In addition, preliminary results suggest that the longer duration of the first coherent percept, an intriguing hallmark of plaid tristable perception, may be due to the slower switching rate of depth ordering. These experimental results suggest a hierarchical architecture and computational models should be able to explain the complex dynamics of plaid tristable perception. Based on this new experimental insight, four architectures of simple competition rate models are currently being tested, and preliminary results suggest that a two layers encoding model could explain important features of this perceptual organization.
Pathological increase of the spectral centroid of resting state BOLD signal from the salience network in MDD

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Interregional functional connectivity (FC) is viewed as a prerequisite of large-scale communication of neuronal assemblies. FC is calculated as a measure reflecting signal covariance, i.e. synchronous signal development over time. This can only occur when dominant frequencies of the time courses are identical, because otherwise signal would naturally diverge at significant periods of time. Numerous evidences hint at differential functional contributions of processes reflected by segregated spectral ranges of fMRI BOLD fluctuations. We investigated spectral contributions to signal from resting state networks in patients with major depressive disorder (MDD) and healthy controls as well as frequency resolved functional connectivity patterns. Specifically, we hypothesized that i) in the salience network in MDD power in higher frequency ranges would be increased, and ii) associated functional connectivity would be affected. We found that the spectral centroids (SC) as aggregate descriptive measures for the frequency spectrum display a distinct grading between RSNs in patients and controls. Similarly, we find a grading of percent signal change (PSC) between the networks. In patients, SC is selectively increased in the salience network (SN), while PSC is increased in occipital networks. Consistently, hubs of functional connectivity differentially expressed across frequencies are significantly dampened in patients in the anterior cingulate cortex (ACC) node of the SN, as well as in primary visual cortex. We conclude that interregional neuronal communication, as expressed via FC measures, operates on different specific time scales. In MDD characteristic fast processes are enhanced or introduced impacting disruptively on large-scale communication.
Novel concept of intrinsic ignition characterises the broadness of communication in different brain states or conditions

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Intrinsic ignition is a novel concept that measures the broadness of propagation of brain activity as a local measure for a given brain area. We applied this new measure to two different sets of resting state functional MRI in order to explore how the human brain develops during early adulthood and its relationship with intelligence. Our work suggests that some areas could still be developing their efficiency of communication with the rest of the areas of the brain during that stage. Using a whole-brain computational model we also show that there is a clear change in the optimal working point of the brain understood as complex network and a dynamical system, during this development stage. We also provide some evidence that could suggest that intrinsic ignition can give very relevant insights to the knowledge of intelligence. Indeed, when we compare groups with low and high levels of intelligence we observe robust differences. Furthermore, we show that those differences might arise from different hierarchies of computation, defined as the distribution of ignition capabilities of the different regions of the brain.
**Bistability and complexity within the sleeping brain: simultaneous intracranial EEG and high-density scalp EEG recording**


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The clinical evaluation of disorders of consciousness (DOCs) in severely brain-injured patients relies on their ability to connect to the surrounding environment and demonstrate their subjective experience through motor behavior. To overcome this clinical problem, it has been recently developed a theory-driven, objective measure of the level of consciousness (Perturbational Complexity Index - PCI) calculated as the algorithmic complexity of the spatiotemporal pattern of the cortical responses obtained by perturbing the cortex with transcranial magnetic stimulation (TMS) (Casali et al. Sci Tr Med 2014). In awake healthy subjects, the EEG response to TMS (TMS evoked potentials - TEPs) show multiple components possibly reflecting recurrent and causal interactions among different cortical areas (Sarasso Clin EEG Neurosci 2014) and results in high values of PCI. On the contrary, in vegetative state patients as well as in anesthesia and during the deepest stages of sleep (non-REM sleep), TEPs results in a positive-negative deflection highly resembling sleep slow-waves (Massimini et al. Science, Rosanova et al. Brain, Sarasso et al. Curr Bio) associated to low values of PCI. It is well known that spontaneous sleep slow-waves emerge from the bistable dynamics given by the alternation of neuronal intense firing (up-states) and silence (down-states) (Steriade J Neurosci 1993, McCully Nat Com 2017). It has been suggested, by means of intracranial electrical stimulation and recordings, that neuronal bistability could be responsible for loss of complexity in non-REM sleep (Pigorini et al. NeuroImage 2015). However, a direct link between bistability and loss of complexity is still missing. To this aim, the present work combines intracortical single pulse electrical stimulation (SPES) in humans undergoing pre-surgical evaluation, simultaneous intracortical recordings (stereo-EEG) and scalp high-density electroencephalography (hd-EEG, 256 channels). Preliminary results show that during wakefulness the complex spatiotemporal dynamics observable at the scalp level are sustained by recurrent, causal interactions among different cortical areas. During non-REM sleep, when consciousness fades, the occurrence of cortical down-states after a transient activation (i.e. bistability) prevents the emergence of stable patterns of causal interactions leading to low PCI at the scalp level. Although very preliminary, these results draw a first link between local bistable dynamics characterizing cortical neurons during sleep and loss of complexity, a theoretical requirement for consciousness. Future studies should investigate whether sleep-like mechanism may account for the collapse of thalamocortical complexity detected by perturbations in pathological conditions such as in the DOCs patients.
Biomarkers for Treatment Resistant Depression

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Introduction
Treatment resistant depression is a term used in clinical psychiatry to describe cases of major depressive disorder (MDD) that do not respond adequately to appropriate courses of at least two antidepressants. In fact, a significant proportion of patients with major depressive disorder (MDD) fail to achieve remission with standard antidepressant therapies, even when optimally delivered. These patients are classified as treatment-resistant depression (TRD), which is distinguished from "difficult-to-treat" depression, defined as depression treated under circumstances that precludes the optimal delivery of a potentially beneficial treatment such as sub-therapeutic dosing, intolerable side effects and poor adherence. TRD is also distinguished from severe depression, as some patients with milder depressive symptoms are markedly treatment resistant, whereas others with profound, acute depressive symptoms are quite treatment responsive. Defining the boundaries of TRD is critical from a clinical, research, and public health perspective, as drug and device manufacturers seek new regulatory approvals for numerous indications in the TRD spectrum. In our study we are going to look for proteins with altered plasma levels in TRD patients compared to MDD patients and healthy control. Ultimately aiming at developing quantitative objective diagnostic tools, in our study we are going to look for biological signatures for Treatment Resistant Depression; proteins with altered plasma levels, micro-RNA polymorphisms and gene expression profiles in TRD patients and to compare them to MDD patients and healthy controls. Methods one hundred twenty blood samples were obtained from TRD patients, plasma was separated and stored in (-80). Protein levels, gene expression profiling and miRNA polymorphisms will be examined. (these will be started sooner, that is why abstract is lacking further methods, results and conclusions.)
The impact of music on the brainwave oscillations in children

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Motivation

The purpose of this study was to investigate the impact of music on the bioelectrical activity of the brain in children with genetic epilepsy and in healthy control group.

Methods

The prospective randomised study was carried out in the Department of Neurology, in Children’s Hospital, Affiliate of Vilnius University Hospital Santaros klinikos.

Children with generalised or focal genetic epilepsy and also healthy controls were investigated. All patients underwent electroencephalograms with auditory stimulation of W. A. Mozart’s Sonata for Two Pianos in D major, K.448. The absolute spectral power of brainwaves in delta (1-4Hz), theta (4-8Hz), alpha (8-13Hz) and beta (13-25Hz) frequencies in both periods of silence and music was compared. The data was analysed in all electrodes together (hereinafter referred as E), as well as in groups of electrodes: frontal (F), central (C), temporal (T), parietal (P) and occipital (O). Demographic and clinical data of the patients were also analysed. Data analysis was carried out using Matlab software with EEGLAB toolbox.

Results

Data of 52 patients, aged 12.2 ± 3.7 years old, 28 females, 24 males was analysed. There were 32 patients in the epilepsy group (18 with focal and 14 with generalised epilepsy) and 20 healthy controls. There was no statistically significant difference between the demographic data of the groups.

Comparing the periods of silence and music, the epilepsy group had a significantly reduced absolute brainwave power during music in theta (E, P, O), alpha (E, F, P, T, O) and beta (E, P, O) frequencies. In the control group, the absolute brainwave power also reduced in delta (P, O), theta (E, F, P, T, O), alpha (E, F, P, T, O), beta (E, P, T, O) frequencies while listening to music. No significant correlations with age, gender, type of epilepsy or antiepileptic medications were observed.

Discussion

Listening to music significantly reduced absolute brainwave power both in epilepsy and control groups, mostly in parietal and occipital areas. However, this effect included a wider range of frequencies and electrode groups in the control group. To better understand this phenomenon, a further investigation of the differences in the brainwave oscillations between healthy population and patients with epilepsy would be needed.
Context-based Normalization of Histological Stains using Deep Convolutional Features

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While human observers are able to cope with variations in color and appearance of histological stains, digital pathology algorithms commonly require a well-normalized setting to achieve peak performance, especially when a limited amount of labeled data is available. This work provides a fully automated, end-to-end learning-based setup for normalizing histological stains, which considers the texture context of the tissue. We introduce Feature Aware Normalization, which extends the framework of batch normalization in combination with gating elements from Long Short-Term Memory units for normalization among different spatial regions of interest. By incorporating a pretrained deep neural network as a feature extractor steering a pixelwise processing pipeline, we achieve excellent normalization results and ensure a consistent representation of color and texture. The evaluation comprises a comparison of color histogram deviations, structural similarity and measures the color volume obtained by the different methods.


Demos: https://stes.github.io/fan
The Reorganization of Functional Architecture in the Early Stages of Parkinson's Disease

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Introduction: The aim of this study was to identify longitudinal abnormalities of functional connectivity and its relation with motor disability in early to moderately advanced stages of Parkinson’s disease patients.

Methods: 3.0T structural and resting-state functional MRI was performed in Parkinson’s disease patients (n=16) with mean disease duration of 2.2 ± 1.2 years at baseline with a clinical follow-up of 1.5 ± 0.3 years and in healthy subjects (n=16). Resting-state fMRI analysis included computation of region-to-region connectivity, correlation with UPDRS#III scores and computation of Global Efficiency and Degree Centrality.

Results: At baseline, patients showed connectivity increase between the cerebellum and the somatomotor network, and decrease in motor regions (Rolandic operculum, precentral gyrus, supplementary motor area, postcentral gyrus) and in cingulate connectivity. At 1.5 years follow-up, connectivity remained altered in same regions identified at baseline. The cerebellum showed additional hyperconnectivity within itself and had increased connectivity with the caudate nucleus, thalamus and amygdala when compared to controls. These differences correlated with UPDRS-III scores. Seed-based connectivity revealed increased involvement of default mode network with precentral gyrus at follow-up in the patients.

Conclusion: The study revealed marked disturbances of the overall architecture of connectivity. The noted alterations in cortical motor areas were associated with cerebellar hyperconnectivity in early to moderately advanced stages of Parkinson’s disease which is suggestive of ongoing attempts of recovery and compensatory mechanism for an affected function. The potential of identified connectivity alterations in regions related to both motor and attentional functions need further evaluation as objective markers to monitor disease progression, and medical, as well as surgical interventions.